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EXAMINER	
SHEIKH, HUMERA N	

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1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,906	OSHLACK ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-86,89 and 91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-86,89 and 91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/8/08;2/24/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Applicant's election without traverse of Group I (claims 75-86, 89 & 91) in the reply filed on 02 January 2009 is acknowledged. Acknowledgement is also made of the Request for Continued Examination (RCE) under 37 CFR 1.114, the Amendment and Applicant's Arguments/Remarks, all filed 09/08/08. Submission of the Information Disclosure Statements (IDS) filed 09/08/08 and 02/24/09 is also acknowledged.

Applicant has overcome the following rejections by virtue of the amendment to the claims: (1) The 35 U.S.C. §112, first and second paragraph rejections for claim 75 have been withdrawn; (2) The 35 U.S.C. §103(a) rejection of claims 75-86 over Palermo (WO 99/32120) has been withdrawn; (3) The 35 U.S.C. §103(a) rejection of claims 75-86 over O'Malley et al. (U.S. Pat. No. 6,004,970) in view of Palermo (WO 99/32120) has been withdrawn; (4) The 35 U.S.C. §103(a) rejection of claims 75-86 over O'Malley et al. (U.S. Pat. No. 6,004,970) in view of Whitmire (U.S. Pat. No. 6,120,806) has been withdrawn.

Claims 75-86, 89 and 91 are pending in this action. Claims 75-82, 84 and 85 have been amended. Claims 1-74, 87, 88 and 90 have been cancelled. Claims 75-86, 89 and 91 are rejected.

* * * * *

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e)

has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08 September 2008 has been entered.

* * * * *

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75 and 85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Namely, claim 85 which recites language drawn to the "prevention of euphorigenic effects" renders the claims non-enabling. The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention/(5) The breadth of the claims:

The nature of the invention is directed to a dosage form comprising particles consisting of an opioid antagonist, a means for sequestering the opioid antagonist and one or more pharmaceutical excipients, whereby the dosage form is an oral dosage form and whereby if the

dosage form is subjected to tampering, such as by crushing, chewing, grinding, etc., will produce a physiological effect. The claims are quite broad and permit additional components (i.e., auxiliaries, excipients, additional active agents) in the dosage form. Furthermore, the claims do not recite specific ingredients, such as a specific hydrophobic material, which is used as the 'sequestering means'.

(2) The state of the prior art:

The prior art teachings provide for compositions comprising the use of opioid antagonists, opioid agonists and sustained release coating materials. The compositions can be in various forms, which include, tablets, capsules, lozenges, emulsions and the like (see for instance, Palermo WO 99/32120).

(3) The relative skill of those in the art:

The relative skill of those in the art is high, such as Ph.D. or M.D. level technology.

(6) The amount of direction or guidance presented:

The specification filed 11/04/03, discloses 'that the physiological effect is the prevention of euphorigenic effects'. It is unclear to the Examiner as to how the instant invention can "prevent" such euphorigenic effects using the composition claimed herein. The specification establishes that various unique and specific ingredients are combined to result in the instant dosage form in order to avoid the "euphorigenic effects". However, the claim limitation of the "prevention of euphorigenic effects" renders the claims non-enabling since the specification provides no guidance on how the prevention of these effects would be provided through the use of merely an antagonist, a means for sequestering and an optional pharmaceutical excipient, as is instantly claimed (see claim 75 for instance).

(7) The presence or absence of working examples:

The working examples are insufficient to establish the instant "prevention of euphorigenic effects". The examples are distinct from the scope of the claims and there are no formulations of the claims presented which would be representative of the examples shown in the instant specification.

(8) The quantity of experimentation necessary:

When the above factors are weighed together, it is the position of the Examiner that the instant invention would require 'undue' and painstaking experimentation to arrive at the instant invention to determine which particular combination of ingredients and in which particular amounts and/or ratios would be needed to "prevent" euphorigenic effects as is instantly claimed by Applicant.

It is suggested that the limitation "prevention of euphorigenic effects of opioids" be deleted to overcome this rejection.

* * * * *

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 82 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 82 recites the limitation "the opioid agonist" in line 2. There is insufficient antecedent basis for this limitation in the claim.

* * * * *

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 75-79, 83-86, 89 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kreek et al. (U.S. Pat. No. 4,987,136).

Kreek et al. ('136) teach oral sustained release dosage forms that comprise effective amounts of an opioid antagonist, such as naloxone, naltrexone, nalmefine and related compounds (col. 1, lines 59-66); (col. 2, lines 4-62).

Polymeric carriers are disclosed that include carnauba wax, cellulose esters and ethers, fats, keratin, gluten or various natural or synthetic esters (col. 5, lines 63-68). The polymeric carrier is comprised in amounts of from about 80% to 95% (col. 6, lines 58-65).

Kreek teaches sustained release forms of the medicament, which can deliver 10 to 50 mg of medicament per day and over selected periods of time, for example 4 to 12 hours (col. 2, lines 4-10).

With regards to the ratios claimed, it is the position of the Examiner that no unexpected results accrue from the instant ratios claimed, as these are variable parameters that can be attained using routine experimentation.

With respect to the claim limitations drawn to the dosage form "not posing a risk of precipitation of withdrawal" and "the opioid antagonist not being bioavailable when the dosage form is intact" (claims 83 & 84 respectively), the Examiner notes that these are future-intended use limitations, which do not accord patentable weight to the claims.

The instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, given the explicit teachings of Kreek et al.

* * * * *

Claims 75-86, 89 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaiko *et al.* (hereinafter "Kaiko") (U.S. Pat. No. 6,277,384).

Kaiko ('384) teaches oral dosage forms comprising a combination of an orally analgesically effective amount of an opioid agonist and an orally active opioid antagonist, the opioid antagonist being included in a ratio to the opioid agonist to provide a combination product which is analgesically effective when the combination is administered orally, but which is aversive in a physically dependent subject (see Abstract); (col. 5, lines 1-18). Kaiko also teaches a method of treating pain comprising the opioid agonist (analgesic) which reducing the abuse potential of the dosage form (column 4, lines 46-67). The method for treatment comprises orally administering an orally analgesically effective amount of an opioid agonist together with an opioid antagonist in a ratio which maintains analgesic efficacy by the opioid analgesic but which may decrease analgesia somewhat by direct measurement in patients or by the use of one or more surrogate measures of opioid effect in human subjects (col. 5, lines 58-64).

Suitable opioid agonists taught include hydrocodone (col. 5, lines 33-37). Additional analgesics are taught at column 11, lines 34-65. Suitable antagonists disclosed include for example, naltrexone (col. 5, lines 33-37). Other antagonists disclosed include naloxone, nalmephene, cyclazocine and levallorphan (col. 10, lines 3-29).

The pharmaceutical compositions may be in the form of tablets, multiparticulate formulations, powders, granules, matrix spheroids or coated inert beads and the like (col. 7, lines 18-27). The dosage forms may provide an immediate release of the opioid agonist and opioid antagonist. In certain embodiments, the dosage forms provide a sustained release of the opioid agonist, and provide the part or all of the dose of the opioid antagonist in (i) immediate release form; (ii) sustained release form or (iii) both immediate release and sustained release form. Sustained release may be accomplished, e.g., via a sustained release carrier into a matrix containing the opioid agonist and opioid antagonist or via a sustained release coating of a matrix containing the opioid agonist and opioid antagonist (col. 7, lines 27-42).

In preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the opioid analgesic is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer or (iii) mixtures thereof (col. 17, lines 28-54). For instance, the hydrophobic material can be used to coat inert pharmaceutical beads such as non-pareil beads (col. 19, lines 45-53). Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, non-pareil beads. The resultant coated substrate (i.e., beads) may then be optionally overcoated with a barrier agent to separate the therapeutically active agent from the hydrophobic controlled release coating. The beads may then be overcoated with an aqueous dispersion of the hydrophobic material (col. 20, lines 1-29). A combination of two ore more hydrophobic materials can be used (col. 22, lines 56-62).

Suitable and preferred alkylcellulose polymers taught include ethylcellulose (col. 17, lines 46-54). Acrylic polymers are also disclosed and include acrylic acid and methacrylic acid

copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid) and the like (col. 18, line 9 – col. 19, line 23). Plasticizers can also be included in the composition col. 19, lines 24-41). A process for preparing coated beads is disclosed at column 19, lines 46-67. Hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials and any pharmaceutically acceptable hydrophobic material or hydrophilic material, which is capable of imparting, controlled release of the active agent and which melts (or softens to the extent necessary to be extruded) may be used in this invention (col. 21, lines 50-57).

Kaiko teaches that the abuse potential of opioid analgesics is surprisingly curtailed by their invention. It is possible to combine in a single oral dosage form an opioid analgesic together with a small amount of opioid antagonist to achieve a product which still provides analgesia but which substantially negates the possibility that a physically dependent human subject will continue to abuse the drug by taking more than one tablet at a time, e.g., 2-3 times more than the usually prescribed dose (col. 13, lines 37-61).

With regards to amounts of hydrophobic material claimed, the Examiner notes that suitable or effective amounts can be determined by one of ordinary skill in the art through routine or manipulative experimentation to obtain optimal results as these are variable parameters attainable within the art. Moreover, generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Furthermore, Kaiko teaches that their controlled release profile can be altered, for example, by varying the amount of overcoating with the hydrophobic material (col. 19, lines 54-67).

With respect to the instant dosage form, which recites "a dosage form comprising" the "comprising" claim language permits the presence of additional components and agents, including the additional "opioid agonists" of Kaiko. Moreover, it is noted that Applicants themselves permit and desire the inclusion of opioid agonists as is disclosed and recited in instant claims 80-81, for example.

Regarding the limitation of "means for sequestering comprising a layer comprising a hydrophobic material", it is noted that Kaiko does teach the use of an overcoating with a barrier agent, for instance, to separate the therapeutically active agent from the hydrophobic controlled release coating. The beads may then be overcoated with an aqueous dispersion of the hydrophobic material (col. 20, lines 1-29). While Kaiko does not indicate that their hydrophobic material/coating (i.e., sequestering material) is provided in a way so as to separate the antagonist from the opioid agonist, it is the position of the Examiner that the prior art does not have to teach this property (separation of agonist from antagonist), but merely that the prior art suggest using the material (hydrophobic material) for any reason. In this instance, since the art does clearly suggest use of the same hydrophobic coating materials (i.e., Applicant's sequestering material) used in the same field of endeavor as the Applicant, burden would be shifted to Applicant to show that the hydrophobic coating materials disclosed by the prior art would not be suitable for their intended function.

With respect to the effects produced by the opioid antagonist, such as when the dosage is intact or alternatively, tampered with, Kaiko sufficiently meets these limitations. Kaiko teaches

that their dosage forms resist abuse potential and can provide an aversive experience when a large amount of the combination product, e.g., about 2-3 times the usual prescribed dose, is taken by or administered to a physically dependent subject. Furthermore, the use of opioid antagonists (i.e., naltrexone) are known to prevent euphorigenic effects of the opioid agonists and also provide a blocking action.

Pertaining to instant claims 75, 89 and 91, which present particular ratios and/or release of the antagonist when the dosage form is intact versus when the dosage form is tampered with, Kaiko teaches suitable weight ratios for the opioid agonist:antagonist components but does not explicitly teach Applicant's ratios. However, it is the position of the Examiner that the determination of effective or suitable ratios is within the level of one of ordinary skill in the art through routine experimentation to obtain optimal results, since these are variable parameters attainable within the art.

With regards to the recitation of an opioid antagonist that is "sequestered", the term "sequestered", even as defined by Applicant's specification, merely requires that the formulation at some point in time be non-releasable (see specification, page 5, lines 23-31). The formulations containing opioid antagonists as disclosed by Kaiko would function in the same manner as instantly desired, such as in blocking or reversing the effects of the opioid agonists to avoid or resist misuse and abuse. Hence, no distinction has been observed that would result in a *patentable* distinction based on the instant antagonist versus those (antagonists) disclosed by the art.

* * * * *

Claims 75-86, 89 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuczynski *et al.* (hereinafter "Kuczynski") (WO 97/33566).

Kuczynski ('566) teaches an oral dosage form and method of administering a dosage form comprising an opioid antagonist for lessening the incidence of drug abuse or substantially preventing opioid abuse. The dosage form comprises a first composition containing an opioid and a second composition separate and distinct from the first composition containing an antagonist for lessening opioid abuse (see page 1, lines 6-10); (p. 2, lines 10-19). The opioid antagonist is included in an effective amount to attenuate or lessen and/or reduce the effect of the opioid in the first composition. The antagonist is present in 10 mg to 275 mg or 0.75 to 10 wt%. Suitable antagonists disclosed include for example, naltrexone, naloxone, nalmephene, nalmexone, nalorphine, nalpuphine, and the pharmaceutically acceptable bases and salts thereof (p. 3, lines 14-23).

The examples at pages 4-12 demonstrate various pharmaceutical compositions of the invention. Example 3, on page 7, for instance, demonstrates a dosage form having a cellulose polymer, such as those disclosed on lines 25-28. Additional cellulose polymers are disclosed in Example 5, on pages 8-9 and include carboxymethylcellulose. The polymer (carboxymethylcellulose) may be provided in amounts of 20-99% (p. 9, lines 3-25; Example 5). The dosage forms may be in the form of a tablet (p. 18, claim 15).

* * * * *

Response to Arguments

Applicant's arguments filed 09/08/08 have been fully considered and were found to be partially persuasive.

- **Rejection under 35 U.S.C. 103(a) over Palermo (WO '120):**

Applicant argued," Applicants submit the 'consisting of' language excludes the presence of the opioid agonist in the particles of claim 75. Palermo requires at least a two-step extraction process to separate the opioid agonist from the opioid antagonist."

This argument was found persuasive based on the amendment to the claims. Accordingly, the 35 U.S.C. §103(a) rejection over Palermo has been withdrawn.

- **Rejection under 35 U.S.C. 103(a) over O'Malley et al. (USPN 6,004,970) in view of Whitmere (USPN 6,120,806) OR Palermo (WO '120):**

Applicant argued," The O'Malley patent describes treatment of nicotine dependency by administration of an opioid antagonist. O'Malley does not teach or suggest a dosage form comprising particles of the opioid antagonist that are sequestered such that an amount of the opioid antagonist released from the untampered dosage form is insufficient to produce a physiological effect."

This argument was found persuasive based on the amendment to the claims. Accordingly, the 35 U.S.C. §103(a) rejection over O'Malley in view of Whitmere or Palermo has been withdrawn.

Rejection under 35 U.S.C. 103(a) over Kreek et al. (USPN 4,897,136):

Applicant argued, "The Kreek patent does not teach or suggest a dosage form comprising particles of the opioid antagonist that are sequestered such that an amount of the opioid antagonist released from the untampered dosage form is insufficient to produce a physiological effect of the opioid antagonist in a human patient."

This argument was not deemed persuasive. Kreek teaches oral sustained release dosage forms that comprise effective amounts of an opioid antagonist, such as naloxone, naltrexone, nalmefine and related compounds (col. 1, lines 59-66); (col. 2, lines 4-62). Kreek teaches that suitable forms of the medicament include sustained release forms, which can deliver over selected periods of time, for example 4 to 12 hours (col. 2, lines 4-10). It is noted that no particular degree of sequestration is recited in the instant claims. Moreover, the difference, even if recited, would be only a difference in degree and not of kind. It is the position of the Examiner that Applicant has not established that the instant invention would be materially different than the compositions of the art, which teaches use of the same components, in a similar manner to yield similar effects and results as that desired by Applicant.

Conclusion

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday-Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Humera N. Sheikh/

Primary Examiner, Art Unit 1615

hns

March 16, 2009